Journal of Forensic and Legal Medicine 19 (2012) 312–315

Contents lists available at SciVerse ScienceDirect

Journal of Forensic and Legal Medicine

journal homepage: www.elsevier.com/locate/jflm

Case review

Marantic endocarditis – A not so benign entity

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ARTICLE INFO

Article history:
Received 18 January 2012
Accepted 15 February 2012
Available online 5 March 2012

Keywords:
Marantic endocarditis
Sudden death
Forensic
Coronary artery embolus
Infarct

ABSTRACT

Marantic, verrucous or nonbacterial thrombotic endocarditis, is characterised by the deposition of an amorphous mixture of fibrin and platelets onto heart valves. Although not commonly a cause of death in forensic practice, it may be associated with systemic embolisation. This was observed in a 60-year-old woman who suddenly collapsed and was found at autopsy to have a poorly differentiated adenocarcinoma of the lung with vegetations from marantic endocarditis on the mitral valve and embolisation with infarcts in the left kidney, the spleen, the right occipital cortex of the brain and the left ventricle of the heart. Death was due to coronary artery embolism from marantic endocarditis associated with an undiagnosed adenocarcinoma of the lung. Although marantic endocarditis is more common in hospital autopsies than in forensic cases, it can have lethal complications that result in sudden and unexpected death. Histories of debilitating disease and/or arterial thromboembolic episodes necessitate meticulous examination of the cardiac valves with careful serial sectioning of the major epicardial coronary arteries and histologic sampling of both ventricles.

1. Introduction

Marantic endocarditis, also known as nonbacterial thrombotic endocarditis, is characterised by the deposition of an amorphous mixture of fibrin, platelets and red blood cells onto heart valves.[1] These vegetations are sterile and are not associated with bacteraemia or destructive changes of the underlying valve.[2] Marantic endocarditis has a low incidence of between 0.9 and 1.6% in adult autopsy populations.[3]

Although not commonly encountered as a cause of death in forensic practice, marantic endocarditis has a relatively high incidence of systemic embolic events (in 42% of cases).[4] Arterial embolisation causes infarcts predominantly within the brain, spleen and kidney.[1,5] Less commonly, embolisation occurs into the coronary artery circulation.[1,6,7] The following case details a patient with an occult adenocarcinoma of the lung who died unexpectedly from a myocardial infarct that had been caused by embolism into the smaller braches of the coronary arteries from undiagnosed marantic endocarditis.

2. Case report

A 60-year-old woman had been unwell for several weeks. A chest CT had revealed an area of opacity in the lower lobe of the left lung and an ultrasound showed thickening of the gallbladder wall. She was commenced on antibiotics with no improvement. She next presented to hospital with left-sided chest pain, fever and confusion, and soon after suffered a cardiac arrest. Resuscitation was unsuccessful.

At autopsy a poorly differentiated adenocarcinoma measuring 4 × 2 × 2 cm was located in an area of subpleural scarring in the posterior aspect of the lower lobe of the left lung (Fig. 1) with metastases in the left hilar lymph nodes. Within the heart a row of bland vegetations was present along the line of closure of the mitral valve leaflets which ranged in size from a few millimetres to 12 mm (Fig. 2). There was evidence of systemic embolisation with two infarcts in the left kidney, the spleen (Fig. 3) and the right occipital cortex of the brain.

In addition, there was pallor over the apical aspect of the left ventricle of the heart. The coronary arteries did not show significant atherosclerotic narrowing. Histologically, fragments of embolized vegetations were identified within smaller intramural arteries (Fig. 4) with patchy areas of organizing infarcts throughout the left ventricle (Fig. 5). No bacteria were identified within the vegetations which were composed of an admixture of fibrin and

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1752-928X/$ – see front matter
doi:10.1016/j.jflm.2012.02.021

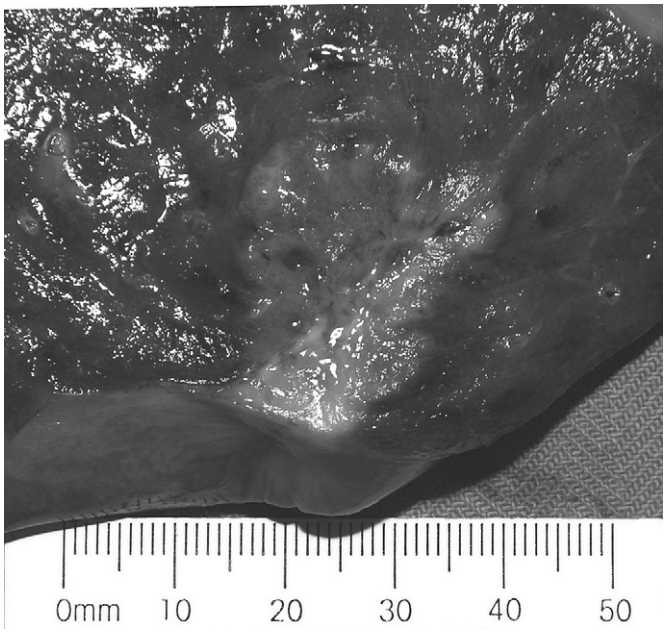

Fig. 1. Occult adenocarcinoma of the lung associated with marantic endocarditis.

platelets (Fig. 6). Although no major arterial occlusion was identified on careful serial sectioning of the major epicardial coronary arteries, the findings were of myocardial ischaemia due to microemboli arising from vegetations on the mitral valve. Death was, therefore, caused by coronary artery embolism from marantic endocarditis of the mitral valve associated with poorly differentiated adenocarcinoma of the lung.

3. Discussion

Marantic endocarditis most frequently occurs in individuals between the fourth and eighth decades of life with no sex predilection.[3] It is associated with neoplasms such as mucin-producing adenocarcinomas (as in the reported case), coagulopathies such as disseminated intravascular coagulation (DIC), septicaemia, infections and severe burns.[4] Managing the underlying disease

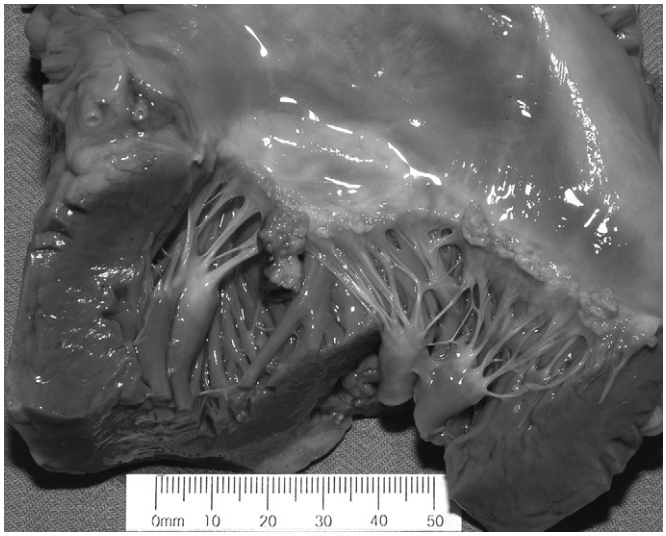

Fig. 2. Irregular vegetations along the line of closure of the mitral valve leaflets.

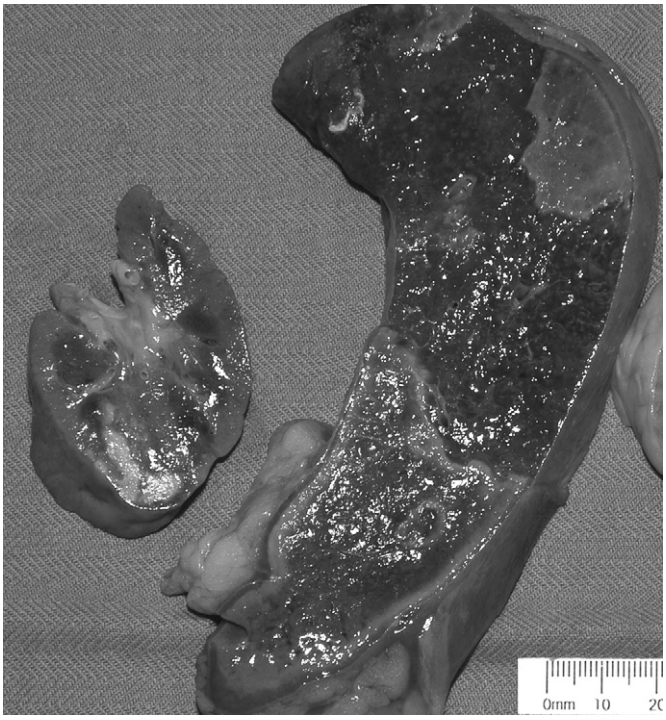

Fig. 3. Infarcts of the spleen and kidney due to embolisation from the mitral valve vegetations.

associated with marantic endocarditis and systemic anticoagulation are currently the only forms of treatment.[1] However, treatment rarely occurs early enough to result in a cure as the diagnosis may be delayed, as was demonstrated in the current case.[7]

Valvular vegetations in marantic endocarditis are usually small, broad based and irregularly shaped (see Fig. 2). These non-infective thrombi are usually located along the line of closure of leaflets or cusps. The majority (82%) of the affected valves in marantic endocarditis are normal and undamaged.[6] The vegetations in marantic endocarditis consist of degenerating platelets interwoven with strands of fibrin and usually range from 0.1 to 2 cm in diameter.[3,6] On histological examination, a bland thrombus, composed of aggregated fibrin and platelets, without an inflammatory reaction or valvular damage, is seen.[6]

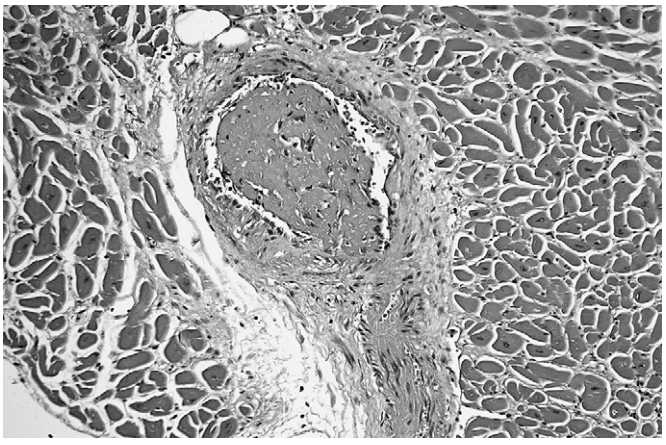

Fig. 4. A fragment of embolised vegetation within a small intramural coronary artery (Haematoxylin and eosin, H&E × 100).

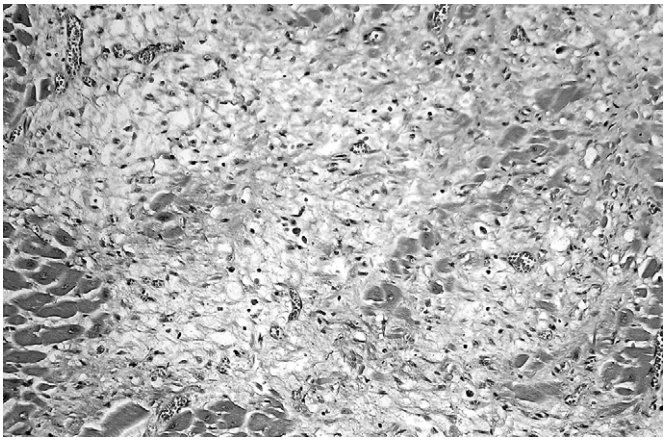

Fig. 5. Patchy areas of organizing infarcts were found throughout the left ventricle (H&E × 100).

Left sided and bilateral vegetations are more consistent with marantic endocarditis than with the other major cause of vegetations, infective endocarditis.[8] Unlike marantic endocarditis, infective endocarditis is an infection of the endocardium which is frequently caused by bacteria such as *Staphylococcus aureus* and *Streptococcus viridans*, and occasionally fungi. The organisms induce platelet aggregation and activate the clotting cascade, leading to the deposition of fibrin and bacteria.[9] Such infected vegetations can embolize leading to complications such as mycotic aneurysms which may cause vascular rupture, local sepsis, and abscesses.[9] Other smaller non-infective vegetations may occur in rheumatic fever and systemic lupus erythematosus.[10,11]

Since vegetations in marantic endocarditis have little inflammatory reaction at the site of attachment, they can detach more readily than vegetations in infective endocarditis and thus cause multiple organ embolism.[3] Systemic embolisation is the main clinical consequence, occurring in 40% of patients.[7] Heart murmurs are rarely heard as the vegetations are small and do not interfere with valve function.[12] The valves most often affected are the aortic, the mitral and a combination of the aortic and mitral.[1] However, the tricuspid and pulmonary valves may also be involved.[5]

Clinically silent embolic events can occur, as small, friable vegetations may not be identifiable by echocardiography. Thus, marantic endocarditis is often only diagnosed at post-mortem examination.[13] At the time of autopsy, approximately 1.2% of patients may have vegetations due to marantic endocarditis.[5]

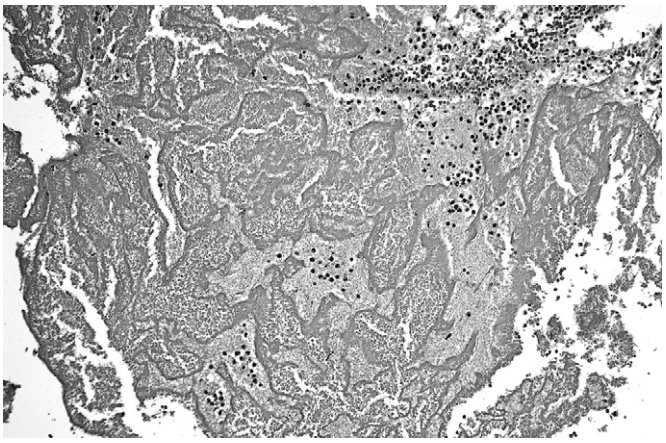

Fig. 6. The mitral valve vegetations composed of an admixture of fibrin and platelets (H&E × 100).

The most common clinical manifestation of marantic endocarditis is stroke, usually affecting the middle cerebral artery territory and often involving both hemispheres. The incidence of stroke in patients with infective endocarditis of 19% is significantly lower than in those with marantic endocarditis (33%).[6] Strokes from infective endocarditis are often single whereas strokes due to marantic endocarditis are often multiple and of varying sizes. Recurrent emboli are a significant indicator of marantic endocarditis, and occur in up to 50% of affected patients. Cutaneous manifestations and a history of psychotic illness may also indicate marantic endocarditis.[3] In patients with associated DIC,[14] there may be haemorrhagic or thrombotic complications.

A much less common complication of marantic endocarditis is coronary embolisation, which may be indicated by a history of chest pain, or documented transient elevations of cardiac enzymes or a new heart murmur.[13] In marantic endocarditis 7.5% of patients have coronary emboli that cause myocardial infarction. In contrast, the incidence of myocardial infarction in patients with infective endocarditis is only 2.9%[6]. Rarely, coronary artery thromboembolism may complicate other condiitons such as rheumatic fever and systemic lupus erythematosus that predispose to vegetations.[10,11]

Diagnosing marantic endocarditis secondary to malignancy prior to autopsy requires a high level of suspicion due to the lack of pathognomonic signs and symptoms. For example, a history of cardiac murmurs, which are characteristic of infective endocarditis, is often absent in marantic endocarditis.[8] Haematological and coagulation studies may have been normal but unexpected results should raise the suspicion of marantic endocarditis, especially when infective causes have been ruled out by negative blood cultures, or by a poor response to antibiotic therapy.[8] McKay and Wahler developed a triad to assist in diagnosing marantic endocarditis which consists of a history of a disease known to be associated with marantic endocarditis, a documented heart murmur, and a history of multiple systemic emboli.[3] Situations when there needs to be a high level of suspicion include (i) a patient who was unresponsive to treatment for infective endocarditis, (ii) a patient with a malignancy who developed an acute ischaemic cerebrovascular stroke or neurological deficit, and (iii) a patient with a history of cerebral embolism of unknown aetiology.[3]

While the exact pathogenesis of vegetations in marantic endocarditis is not fully known it is likely that there are a number of complex interacting factors. Marantic endocarditis occurs in 4% of all end stage cancer patients associated with a thrombophilic state known as Trousseau's syndrome.[8,15] Genetic studies have shown that the presence of the MET oncogene promotes the activity of type-1 plasminogen activator inhibitor and cyclooxygenase-2 genes, leading to thrombus formation.[1] Monocytes or macrophages which interact with malignant cells release cytokines including tumour necrosis factor, interleukin-1, and interleukin-6, resulting in endothelial damage which then predisposes to platelet deposition in areas of high blood flow causing thrombus formation.[5] Macrophages that interact with tumour cells also activate the coagulation cascade and synthesise less anticoagulant proteins, such as protein C and antithrombin III, which may contribute to a thrombophilic state in malignancy.[16,17] Tumour cells themselves may produce procoagulant substances such as cysteine proteases and tissue factor; cysteine proteases activate factor V while tissue factor triggers the extrinsic coagulation cascade by activating factor VII, leading to a hypercoagulable state.[16]

Marantic endocarditis may be more common in hospital than in forensic autopsies, however, as the current case demonstrates, it can have lethal complications that result in sudden and unexpected death. In individuals who come to autopsy with histories of debilitating disease and/or arterial thromboembolic episodes, the possibility of marantic endocarditis should be considered and the

cardiac valves closely examined. Coronary artery thromboembolism should be carefully checked for, with careful serial sectioning of the major epicardial coronary arteries and histologic sampling of intramural vesels in both ventricles.

Conflicts of interest

None declared.

Funding

None declared.

Ethical approval

Forensic Science South Australia.

Acknowledgement

We thank the South Australian State Coroner, Mr. Mark Johns, for permission to report selected details of this case.

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